

#### Europäisches Patentamt

Zweigstelle in Den Haag Recherchenabteilung

#### European Patent Office

Branch at The Hague Search division Office européer des brevets

Département à La Haye Division de la recherche

INNOGENETICS N.V.	
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RELGIOUE	

2 2 -05- 2000

Datum/Date

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Zeichen/Ref./R	er. EP99.10	6.FUNG	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°. 99870109.8 – –
Anmelder/Appli		leur/Patentinhaber/Proprietor/Titulaire IETICS N.V.	
			COMMUNICATION
	The Europe	an Patent Office herewith transmit	ts
	X	the European search report	
		the declaration under Rule 45 El	PC
		the partial European search repo	ort under Rule 45 EPC

The following specifications given by the applicant have been approved by the Search Division:

Abstract

Title

Figure

The abstract was modified by the Search Division and the definitive text is attached to this communication.

the supplementary European search report concerning the international application under Article 157(2) EPC relating to the above-mentioned European patent application. Copies of the documents cited in the search report are

The following figure will be published with the abstract, since the Search Division considers that it better characterises the invention than the one indicated by the applicant.

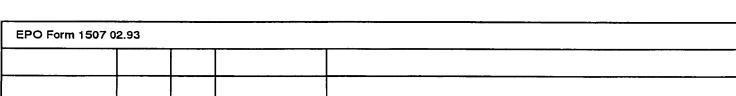
Figure:

enclosed.

Additional copy(copies) of the documents cited in the European search report.

# REFUND OF THE SEARCH FEE

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.







# **EUROPEAN SEARCH REPORT**

**Application Number** 

# EP 99 87 0109 RECEIVED

	DOCUMENTS CONSID	ERED TO BE RELEVANT		FEB <u>0</u> 5 <u>2</u> 01
Category	Citation of document with in of relevant passa	dication, where appropriate, ages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.7) TECH CENTER 1600
X	ENZYME IMMUNOASSAY DNAFROM CANDIDA SPE JOURNAL OF CLINICAL MICROBIOLOGY,US,WAS	HINGTON, DC, pril 1995 (1995-04-01), 2053345	1-3,7,8	C12Q1/68
X	ELIE C M ET AL: "R Candida species wit probes" JOURNAL OF CLINICAL MICROBIOLOGY,US,WAS vol. 36, no. 11, 1 November 1998 (19 3260-3265, XP002086 ISSN: 0095-1137 * the whole documen	HINGTON, DC, 98–11–01), pages 007	1-3,7,8	
X	up to three Candida reaction tube by a using fluorescent D JOURNAL OF CLINICAL vol. 37, no. 1, 199 XP000874684 * see especially pa	MICROBIOLOGY, 9, pages 165-170, ge 166, column 1, n 2, paragraph 2, as	1-3,8	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C12Q
D,X	US 5 426 027 A (LOT 20 June 1995 (1995- * the whole documen		1-3,8	
	The present search report has t	seen drawn up for all claims		
<del></del>	Place of search	Date of completion of the search	<del>'                                    </del>	Examiner
	THE HAGUE	11 February 2000	Kne	hr, M
X : part Y : part docu A : tech O : non	ATEGORY OF CITED DOCUMENTS ticularly relevant if taken alone cicularly relevant if combined with another under the same category noological background the written disclosure rmediate document	T: theory or principle E: earlier patent doc after the filing dat D: document cited in L: document cited fo	cument, but publice en the application or other reasons	shed on, or



# **EUROPEAN SEARCH REPORT**

Application Number EP 99 87 0109

Category		DERED TO BE RELEVANT  n indication, where appropriate,	<del></del>	
Category	of relevant pa	ssages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.7)
X	WO 98 11257 A (SH (US); US HEALTH (I 19 March 1998 (199 * see especially * the whole docume	the claims *	1-3,8	
	hybridization of hybridization with derived from ribos spacers" YEAST,	ANTA R J: "Specific Candida albicans by oligonucleotides comal DNA internal des 709-717, XP000874680	1,3,7,8	
1	WO 99 06596 A (GOV STATE) 11 February * the whole docume	ERNMENT OF THE UNITED 1999 (1999-02-11) nt *	1,3,8	
	SEQUENCING OF FUNG FOR PHYLOGENETICS"	able 1 *	1,2	TECHNICAL FIELDS SEARCHED (Int.CI.7)
	DATABASE GENBANK Accession number ( ZAKIKHANI S AND KA Transcribed spacer Tibosomal cluster of P002130403 Tabstract *	AC): Y14001, 1997 PPE R: "Internal	9,10	
	he present search report has	oeen drawn up for all claims		
	lace of search	Date of completion of the search		Examiner
T	HE HAGUE	11 February 2000	Kneh	r, M
X : particul Y : particul docume A : technok O : non-wri	GORY OF CITED DOCUMENTS and relevant if taken alone any relevant if combined with anothed to the same category opical background then disclosure diate document	L: document cited for	underlying the inve ment, but published the application other reasons	ention ed on, or



# **EUROPEAN SEARCH REPORT**

Application Number EP 99 87 0109

	DOCUMENTS CONSIDI	ERED TO BE RELEVANT		
Category	Citation of document with in of relevant passa	dication, where appropriate, ges	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.CI.7)
D,A	internally transcribilities digestion of fluconal krusei, Candida inconvegensis strains JOURNAL OF CLINICAL MICROBIOLOGY,US,WASH	HINGTON, DC, pril 1997 (1997-04-01), 902086004		
A	WO 96 21741 A (CIBA CORP; SANDHU GURPREE 18 July 1996 (1996-6 * the whole document	CORNING DIAGNOSTICS ET S (US); KLINE BRUCE) 07-18) . *		
				TECHNICAL FIELDS SEARCHED (Int.CI.7)
<del></del>	The present search report has be	en drawn up for all claims		
	Place of search	Date of completion of the search	<del></del>	Examiner
<u> </u>	THE HAGUE	11 February 2000	Kneh	ir, M
X : partice Y : partice docum A : techno O : non-w	FEGORY OF CITED DOCUMENTS  ularly relevant if taken alone ularly relevant if combined with another nent of the same category plogical background ritten disclosure recitate document	L: document cited for	ment, but publish he application other reasons	ed on, or

## ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO.

EP 99 87 0109

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

11-02-2000

Patent document cited in search repo		Publication date		Patent family member(s)	Publication date
US 5426027	Α	20-06-1995	US US US US	5688644 A 5645992 A 5631132 A 5635353 A	18-11-1997 08-07-1997 20-05-1997 03-06-1997
WO 9811257	Α	19-03-1998	AU EP	4482897 A 0927269 A	02-04-1998 07 <b>-</b> 07-1999
WO 9906596	A	11-02-1999	AU EP	8673498 A 0996745 A	22-02-1999 03-05-2000
WO 9621741	Α	18-07-1996	US AU AU BR CA EP JP PL US	5763169 A 5707802 A 693625 B 4313896 A 9607497 A 2209247 A 0804619 A 11500305 T 321139 A 5958693 A	09-06-1998 13-01-1998 02-07-1998 31-07-1996 23-12-1997 18-07-1996 05-11-1997 12-01-1999 24-11-1997 28-09-1999

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# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY	PCT
To: INNOGENETICS N.V. Intellectual Property Dept Industriepark Zwijnaarde 7 B-9052 Ghent BELGIUM	INVITATION TO PAY ADDITIONAL FEES  (PCT Article 17(3)(a) and Rule 40.1)  OUNTIES  19 -12- 2000
	Date of mailing (day/month/year) 15/12/2000
Applicant's or agent's file reference 106-PCT	within 30 MMMs/days from the above date of mailing
International application No. PCT/EP 00/04714	International filing date (day/month/year) 24/05/2000
INNOGENETICS N.V.	
1. This International Searching Authority  (i) considers that there are	mber of) inventions claimed in the international application covered to comply with the requirements of unity of invention the extra sheet:
(ii) X has carried out a partial international search (see Anon those parts of the international application which relate see extra sheet first invention (iii) will establish the international search report on the other part to which, additional fees are paid	to the invention first mentioned in claims Nos.:
The applicant is hereby invited, within the time limit indicated	above, to pay the amount indicated below:
FUR 945,00 x 12  Fee per additional invention number of additional in  Or,x  The applicant is informed that, according to Rule 40.2(c), the pailen, a reasoned statement to the effect that the international apport that the amount of the required additional fee is excessive.	ventions total amount of additional fees
3. Claim(s) Nos	have been found to be unsearchable under and therefore have not been included with any invention.
Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2  NL-2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  Catherine Humbert

International Application No PCT/EP 00/04714

- 1.The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
- 1-5,19-23. 2. This communication is not the international search report which will be established according to Article 18 and Rule 43.
- 3.If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.
- 4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FUJITA S -I ET AL: "MICROTITRATION PLATE ENZYME IMMUNOASSAY TO DETECT PCR-AMPLIFIED DNAFROM CANDIDA SPECIES IN BLOOD" JOURNAL OF CLINICAL MICROBIOLOGY,US,WASHINGTON, DC, vol. 33, no. 4, 1 April 1995 (1995-04-01), pages 962-967, XP002053345 ISSN: 0095-1137 the whole document	1-4,19,
X	ELIE C M ET AL: "Rapid identification of Candida species with species-specific DNA probes" JOURNAL OF CLINICAL MICROBIOLOGY,US,WASHINGTON, DC, vol. 36, no. 11, 1 November 1998 (1998-11-01), pages 3260-3265, XP002086007 ISSN: 0095-1137 the whole document	1-4,19,

o Casaisi	categories of	f aitad	documente	٠
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- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filling date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

International Application No
PCT/EP 00/04714

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
- 1		
X	SHIN J H ET AL.: "Rapid identification of up to three Candida species in a single reaction tube by a 5' exonuclease assay using fluorescent DNA probes" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 37, no. 1, 1999, pages 165-170, XP000874684 * see especially page 166, column 1, paragraph 3 - column 2, paragraph 2, as well as table 1 * the whole document	1-4,20
X	US 5 426 027 A (LOTT TIMOTHY J ET AL) 20 June 1995 (1995-06-20) cited in the application the whole document	1-4,20
X	WO 98 11257 A (SHIN JONG HEE ;REISS ERROL (US); US HEALTH (US); HOLLOWAY BRIAN (U) 19 March 1998 (1998-03-19) * see especially the claims * the whole document	1-4,20
X	BOTELHO A R AND PLANTA R J: "Specific identification of Candida albicans by hybridization with oligonucleotides derived from ribosomal DNA internal spacers" YEAST, vol. 10, 1994, pages 709-717, XP000874680 abstract	1,4,19, 20
X	WO 99 06596 A (GOVERNMENT OF THE UNITED STATE) 11 February 1999 (1999-02-11) cited in the application the whole document	1-4,12,
X	WHITE T ET AL: "AMPLIFICATION AND DIRECT SEQUENCING OF FUNGAL RIBOSOMAL RNA GENES FOR PHYLOGENETICS" US,SAN DIEGO, ACADEMIC PRESS, 1989, pages 315-322, XP002017490 cited in the application * see especially table 1 * the whole document	1-3
Y	DATABASE GENBANK [Online] Accession number (AC): Y14001, 1997 ZAKIKHANI S AND KAPPE R: "Internal transcribed spacers (ITS1) of the ribosomal cluster of Candida albicans" XP002130403 abstract	1-5, 19-22
	<b>-/</b>	•

International Application No
PCT/EP 00/04714

O tonnote	Citation of document with indication where appropriate of the relevant	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE GENBANK [Online] Accession number (AC): Y14002, 1997 ZAKIKHANI S AND KAPPE R: "Internal transcribed spacers (ITS1) of the ribosomal cluster of Candida albicans" XP002153730 abstract	1-5, 19-22
Y	WO 98 50584 A (CHOI JONG SOO ;REISS ERROL (US); GOVERNMENT OF THE UNITED STATE (U) 12 November 1998 (1998-11-12) * see especially the claims * the whole document	1-5, 19-23
Y	LÖFFLER J ET AL.: "Comparison of different methods for extraction of DNA of fungal pathogens from cultures and blood" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 35, no. 12, 1997, pages 3311-3312, XP000961790 cited in the application * see especially page 3311, column 2, paragraph 2 * the whole document	1-4,23
A	WO 95 29260 A (CIBA GEIGY AG ;LIGON JAMES M (CH); BECK JAMES J (US)) 2 November 1995 (1995-11-02) cited in the application the whole document	
Α	JORDAN J A: "PCR identification of four medically important Candida species by using a single primer pair" JOURNAL OF CLINICAL MICROBIOLOGY, vol. 32, no. 12, 1994, pages 2962-2967, XP000961788 cited in the application the whole document	
A	NHO S ET AL: "Species differentiation by internally transcribed spacer PCR and HhaI digestion of fluconazole-resistant Candida krusei, Candida inconspicua, and Candida norvegensis strains" JOURNAL OF CLINICAL MICROBIOLOGY, US, WASHINGTON, DC, vol. 35, no. 4, 1 April 1997 (1997-04-01), pages 1036-1039, XP002086004 ISSN: 0095-1137 cited in the application the whole document	
	-/	

International Application No
PCT/EP 00/04714

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 21741 A (CIBA CORNING DIAGNOSTICS CORP; SANDHU GURPREET S (US); KLINE BRUCE) 18 July 1996 (1996-07-18) the whole document	
,		

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4, 19-23 (partial); 5 (complete)

## **INVENTION 1:**

A method to detect and identify the fungal pathogen Candida albicans in a sample, and an oligonucleotide molecule according to SEQ ID Nos:1-3,33-35, or a variant sequence thereof, suitable for use in such a method.

2. Claims: 1-4, 19-23 (partial); 6 (complete)

#### INVENTION 2:

A method to detect and identify the fungal pathogen Candida parapsilosis in a sample, and an oligonucleotide molecule according to SEQ ID Nos:4-5, or a variant sequence thereof, suitable for use in such a method.

3. Claims: 1-4, 19-23 (partial); 7 (complete)

#### **INVENTION 3:**

A method to detect and identify the fungal pathogen Candida tropicalis in a sample, and an oligonucleotide molecule according to SEQ ID Nos:6,36, or a variant sequence thereof, suitable for use in such a method.

4. Claims: 1-4, 19-23 (partial); 8 (complete)

## **INVENTION 4:**

A method to detect and identify the fungal pathogen Candida kefyr in a sample, and an oligonucleotide molecule according to SEQ ID Nos:7-8, or a variant sequence thereof, suitable for use in such a method.

5. Claims: 1-4, 19-23 (partial); 9 (complete)

#### **INVENTION 5:**

A method to detect and identify the fungal pathogen Candida krusei in a sample, and an oligonucleotide molecule according to SEQ ID Nos:9,37 or a variant sequence thereof, suitable for use in such a method.

6. Claims: 1-4, 19-23 (partial); 10 (complete)

#### **INVENTION 6:**

A method to detect and identify the fungal pathogen Candida glabrata in a sample, and an oligonucleotide molecule according to SEQ ID No:10, or a variant sequence thereof, suitable for use in such a method.

7. Claims: 1-4, 19-23 (partial); 11 (complete)

**INVENTION 7:** 

A method to detect and identify the fungal pathogen Candida dubliniensis in a sample, and an oligonucleotide molecule according to SEQ ID Nos:11-13,38, or a variant sequence thereof, suitable for use in such a method.

8. Claims: 1-3, 12, 19-23 (partial); 13 (complete)

#### **INVENTION 8:**

A method to detect and identify the fungal pathogen Aspergillus flavus in a sample, and an oligonucleotide molecule according to SEQ ID Nos:18-20,42, or a variant sequence thereof, suitable for use in such a method.

9. Claims: 1-3, 12, 19-23 (partial); 14 (complete)

## **INVENTION 9:**

A method to detect and identify the fungal pathogen Aspergillus versicolor in a sample, and an oligonucleotide molecule according to SEQ ID Nos:21,43, or a variant sequence thereof, suitable for use in such a method.

10. Claims: 1-3, 12, 19-23 (partial); 15 (complete)

#### **INVENTION 10:**

A method to detect and identify the fungal pathogen Aspergillus nidulans in a sample, and an oligonucleotide molecule according to SEQ ID Nos:22-25, or a variant sequence thereof, suitable for use in such a method.

11. Claims: 1-3, 12, 19-23 (partial); 16 (complete)

#### **INVENTION 11:**

A method to detect and identify the fungal pathogen Aspergillus fumigatus in a sample, and an oligonucleotide molecule according to SEQ ID Nos:26,27,40,41, or a variant sequence thereof, suitable for use in such a method.

12. Claims: 1-3, 19-23 (partial); 17 (complete)

#### **INVENTION 12:**

A method to detect and identify the fungal pathogen Cryptococcus neoformans in a sample, and an oligonucleotide molecule according to SEQ ID Nos:14-17, or a variant sequence thereof, suitable for use in such a method.

13. Claims: 1-3, 19-23 (partial); 18 (complete)

#### **INVENTION 13:**

A method to detect and identify the fungal pathogen Pneumocystis carinii in a sample, and an oligonucleotide molecule according to SEQ ID Nos:28-32, or a variant sequence thereof, suitable for use in such a method.

- 1. Numerous prior art documents describe PCR primers as well as species-specific oligonucleotide probes, suitable to amplify and hybridize to internal transcribed spacer regions (ITS) deriving from pathogenic fungi. W09811257 (D1) discloses nucleic acid probes for the specific detection of Candida and Aspergillus species, following prior amplification of the ITS1/ITS2 region. Likewise, US5426027 (D2) discloses amplification of the ITS1/ITS2 region from fungi, allowing succeeding probing for Candida albicans as well as for Cryptococcus neoformans. In addition, Botelho and Planta, YEAST, 10, 709-717 '1994! (D3), as well as W09906596 (D4) disclose the specific detection of Candida species using nucleic acid probes deriving from ribosomal internal spacer regions. Finally, W09850584 (D5) discloses specific probing for Aspergillus and other fungi species using probes deriving from the ITS2 region.
- 2. In view of the prior art, the problem of the underlying application can be defined as the provision of further genus— and species—specific probes deriving from the ITS-1 or ITS-2 region, and their use in a method for specifically detecting defined pathogenic fungi.
- 3. Each of the 43 oligonucleotide probes as claimed represent an independent solution concerning the problem of the underlying application. Solution 1 is the provision of SEQ ID NO:1 suitable for the specific detection of Candida albicans. Likewise, solution 2 is the provision of SEQ ID NO:2 suitable for the specific detection of Candida albicans...Finally, solition 43 is the provision of SEQ ID NO:43 suitable for the specific detection of Aspergillus versicolor.
- 4. In view of the fact that oligonucleotide probes specifically suitable within methods for the detection of ITS1 or ITS2 ribosomal regions deriving from pathogenic fungi are already disclosed in the prior art, due to essential differences in primary structure, and due to the fact that the search division could not find any other technical feature which, in the light of the prior art, could be regarded as special technical feature common to these solutions, the ISA is of the opinion that there is no single inventive concept underlying the plurality of 43 solutions of the present application in the sense of rule 13.1 PCT. Consequently, there is a lack of unity, and different inventions, not belonging to a common inventive concept, are formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT.
- 5. However, taking into account the balance between necessary search effort and the levying of additional fees, the ISA has taken the decision to combine oligonucleotide probes suitable for the detection of the very same fungal species (i.e. combining SEQ ID NOS:1-3,33-35, all suitable for the specific detection of Candida albicans) into one group of inventions. The number of (groups of) inventions has therefore been reduced to 13.

# **Patent Family Annex**

Information on patent family members

International Application No
PCT/EP 00/04714

				101711	00/04/14
Patent document cited in search report		Publication date	Patent fami member(s)		Publication date
US 5426027	A	20-06-1995	US 5645 US 5631	644 A 992 A 132 A 353 A	18-11-1997 08-07-1997 20-05-1997 03-06-1997
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